lb. and 165°. The catalyst was removed, and the solvent was distilled at 100° under reduced pressure. The product did not crystallize when it was kept at room temperature for three weeks or at −80° in ether–ligroin for several days. It solidified immediately and completely, however, when it was shaken with 10% aqueous potassium hydroxide. This solidification was caused by hydrate formation, and subsequent lots of the ester rapidly crystallized when they were placed in contact with water and seeded. From a mixture of benzene and ligroin the hydrate separated in the form of shining white plates, m. p. 64–65°.

Anal. Calcd. for $C_{15}H_{19}NO_3 \cdot H_2O$: C, 64.5; H, 7.5. Found: C, 64.9; H, 7.2.

Saponification of the ester with the calculated amount of 2% sodium hydroxide gave **3-benzyl-5-ketonipecotic acid**, colorless plates from 5% acetic acid, m. p. 221–222°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 67.0; H, 6.7. Found: C, 67.1; H, 6.7.

The author thanks Mr. E. E. Renfrew and Mr. S. T. Rolfson for the analyses reported in this paper.

Summary

Reduction of an α-carbethoxy-γ-cyanobutyric ester followed by alkylation of the resulting piperidone, or alkylation of a γ-carbethoxy-γ-cyanobutyric ester followed by reduction, afford methods whereby 3-alkylpiperidones may be prepared.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

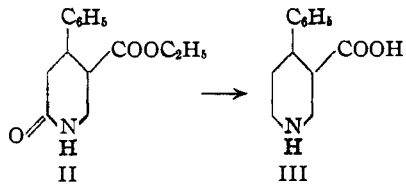
A Synthesis of 4-Phenylpiperidines

BY C. F. KOELSCH

Reactions analogous to those used for the preparation of 3-phenylpiperidines[1] can be used for the preparation of 4-phenylpiperidines. Two routes to the necessary γ-cyano-β-phenylbutyric esters have been investigated. An example of each of these routes is illustrated in the accompanying formulas, and both examples are described in the experimental part of the present paper.

$$C_6H_5CH{=}CHCOOC_2H_5 + CH_2(CN)COOC_2H_5 \longrightarrow C_6H_5CH(CH_2COOC_2H_5)CH(CN)COOC_2H_5 \longrightarrow$$

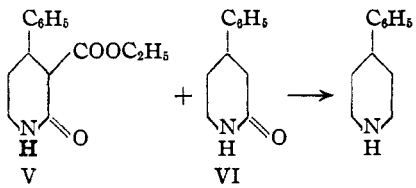
I



II III

$$C_6H_5CH{=}CHCN + CH_2(CO_2H_5)_2 \longrightarrow C_6H_5CH(CH_2CN)CH(COOC_2H_5)_2 \longrightarrow$$

IV



V VI

Experimental

Ethyl 6-Keto-4-phenylnipecotate, II.—The ester I was prepared in 85% yield in one-mole runs, essentially according to the method of Desai[2]; it boiled at 172–175° at 2 mm. It was reduced in an equal weight of alcohol at 140°, using Raney nickel and hydrogen at 2000 lb.; reduction was usually complete after forty-five minutes. The product separated from a mixture of benzene and ligroin in the form of colorless needles, m. p. 91–94°; yield, 67%. A small content of impurity (stereoisomer?) could be removed only by dissolving the substance in warm concentrated sulfuric acid and then reprecipitating it with water; this treatment caused the compound to lose almost no weight, but the recovered substance (II) melted sharply at 102–103°.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9. Found: C, 68.0; H, 7.1.

The ester was hydrolyzed within one minute when it was boiled with 5% aqueous sodium hydroxide. The resulting **6-keto-4-phenylnipecotic acid** separated from water in the form of colorless needles that fell to a white powder when they were dried at 130°; m. p. 214–215°.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.8; H, 5.9. Found: C, 66.0; H, 5.9.

4-Phenylnipecotic Acid, III.—A solution of 20 g. of ethyl 6-keto-4-phenylnipecotate in 200 ml. of dry butyl alcohol was reduced with 20 g. of sodium. Then 150 ml. of water was added, and the resulting layers were separated. The aqueous layer contained 2.5 g. of organic material, from which no pure substance could be isolated. The butyl alcohol layer was brought to *p*H 4 with concd. hydrochloric acid (12 ml.) and then distilled with steam. The aqueous solution remaining was distilled to a volume of 25 ml. and cooled, giving a crystalline deposit (6.8 g.) of the amino acid; it became brown at 270° and melted at 280–285° with decomposition. Since the free acid could not be recrystallized satisfactorily, it was analyzed as its **hydrochloride**, shining tan plates from dilute hydrochloric acid. The salt lost no weight at 130° in a vacuum; it became yellow at 150°, sintered at 250° and melted at 257–259° to a bubble-filled liquid.

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: N, 5.8. Found: N (Dumas), 5.7.

When 4 g. of the amino acid hydrochloride was heated with 12 ml. of 40% formalin in a bath at 100° for forty-eight hours, it was converted into **1-methyl-4-phenylnipecotic acid hydrochloride.** The excess formaldehyde was removed by distilling the mixture to dryness twice with concd. hydrochloric acid, and the amino acid hydrochloride was crystallized from a mixture of alcohol and ether; it weighed 3.5 g. and formed colorless prisms; m. p. 219–222°.

Anal. Calcd. for $C_{13}H_{18}ClNO_2$: C, 61.0; H, 7.0. Found: C, 60.9; H, 7.0.

When the methylated amino acid hydrochloride was boiled with ethyl alcoholic hydrogen chloride for twenty-four hours, it was converted into **ethyl 1-methyl-4-phenylnipecotate hydrochloride,** fine white needles from a mixture of alcohol and ether, m. p. 171–173°.

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.5; H, 7.8. Found: C, 63.6; H, 8.0.

(1) Koelsch, THIS JOURNAL, **65**, 2093 (1943).

(2) Desai, *J. Chem. Soc.*, 1084 (1932).

Ethyl 2-Keto-4-phenylnipecotate, V.—A mixture of 130 g. of cinnamonitrile, 160 g. of ethyl malonate and a solution of 23 g. of sodium in 450 ml. of ethanol was boiled for four hours and then neutralized with dilute acetic acid. The resulting **ethyl α-carbethoxy-γ-cyano-β-phenylbutyrate (IV)** boiled at 190–195° at 0.5 mm. and melted at 43–45°; yield 241 g. (83%).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6. Found: C, 66.5; H, 6.5.

This cyano ester (100 g.) was reduced in an equal weight of alcohol at 155°, using Raney nickel and hydrogen at a pressure of 2000 lb. Removal of the alcohol and solution of the products in benzene gave 50 g. of an uncrystallizable, easily soluble sirup and 17 g. of crystalline **4-phenylpiperidone-2**. The latter substance was also obtained from the sirup by dissolving it in boiling sodium hydroxide solution, acidification, and subsequent distillation of the precipitate under reduced pressure. The lactam formed colorless plates from benzene; m. p. 137–139°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.4; H, 7.4. Found: C, 75.7; H, 7.5.

Twenty grams of 4-phenylpiperidone-2, reduced in butyl alcohol with 20 g. of sodium, gave 11.2 g. of 4-phenylpiperidine, b. p. 137–147° at 21 mm., m. p. 57–60° (reported[3] 57–58°). The hydrochloride of 4-phenylpiperidine sintered at 110° and melted at 164–165° when it was heated slowly; placed in a bath at 150° it melted with effervescence. With the base just described, there was also obtained 2.9 g. of a base that boiled at 160–220° at 18 mm. and melted at 137° after it had been crystallized from benzene; it was not investigated further.

When 8 g. of 4-phenylpiperidine hydrochloride was heated for thirty hours at 100° with an excess of formalin, there was obtained 1.8 g. of a non-volatile base, colorless needles from alcohol, m. p. 101–103° (methylene-bis-4-phenylpiperidine ?), together with 3.1 g. of **1-methyl-4-phenylpiperidine**, a colorless liquid, b. p. 138–140° at 17 mm. The methylated base was analyzed as its **hydrochloride**, colorless plates from a mixture of alcohol and ether, m. p. 185–187°.

Anal. Calcd. for $C_{12}H_{18}ClN$: C, 68.1; H, 8.5. Found: C, 67.9; H, 8.4.

The author thanks Mr. C. H. Stratton for most of the analyses reported in this paper.

(3) Bally, *Ber.*, **20**, 2590 (1887).

Summary

Catalytic reduction of β-phenyl-γ-cyanobutyric esters is accompanied by cyclization and leads to the formation of 4-phenylpiperidones. These lactams can be reduced to 4-phenylpiperidines by treatment with sodium and butyl alcohol.

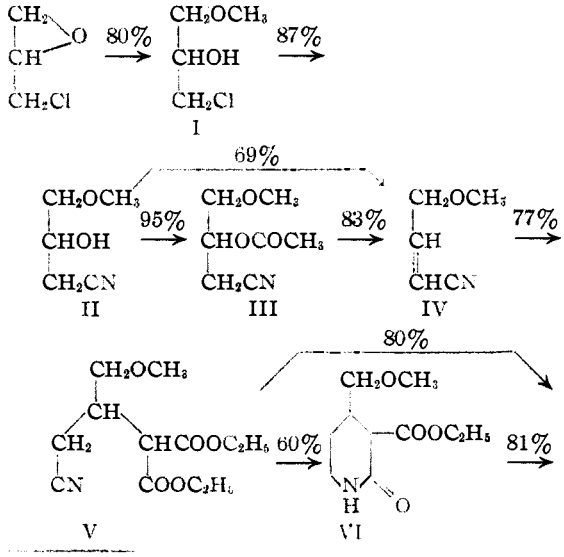
MINNEAPOLIS, MINNESOTA RECEIVED SEPTEMBER 7, 1943

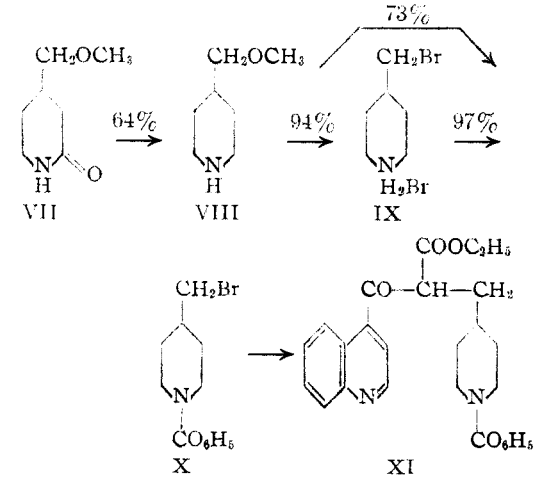
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Two New Syntheses of 1-Benzoylpiperidine-4,β-propionic Acid

BY C. F. KOELSCH

Part I.—The piperidine synthesis described in previous papers[1] can be applied to the preparation of 4-bromomethylpiperidine, and it appeared likely that this halide could be condensed with ethyl quinoline-4,β-ketopropionate to form a compound which occupies a key position in Rabe's[2] synthesis of rubanol-9. The reactions involved and yields realized are summarized in the accompanying chart.





Considerable study was devoted to the determination of the optimum conditions for carrying out each reaction, and satisfactory yields were obtained in each step except the last. Compound X was recovered unchanged after it had been boiled for three hours with the sodium derivative of ethyl quinoline-4,β-ketopropionate in alcohol, and when the period of boiling was prolonged or when ethyl carbonate was used in place of alcohol as the solvent, tarry unworkable products were

(1) Koelsch, THIS JOURNAL, **65**, 2093 (1943); **65**, 2459 (1943).
(2) Rabe, Kindler and Wagner, *Ber.*, **55**, 536 (1922).